Optimizing Clinical and Economic Outcomes in Asthma Management: Individualizing Drug Therapy to Address the Dual Components of Asthma

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Optimizing Clinical and Economic Outcomes in Asthma Management: Individualizing Drug Therapy to Address the Dual Components of Asthma

ROBERT P. NAVARRO, PharmD

INTRODUCTION

Asthma presents important challenges and opportunities for managed care. It remains one of the most common medical conditions with a prevalence of almost 6%. Although we understand the pathophysiology of the disease and its environmental and physiological triggers, the incidence of asthma continues to increase. It consumes increasing amounts of medical resources and negatively impacts the quality of life of patients as well as family members.

The National Heart, Lung, and Blood Institute identified target asthma management outcomes that include no sleep disruption, no missed school or work, minimal need for hospital care, normal activity levels, and near-normal lung function. A survey, however, reveals that 30% to 50% of patients or their families report failure in one or more of these treatment goals. We also have well-accepted NIH treatment guidelines that help categorize the severity of asthma based on symptoms and provide treatment recommendations based on disease severity. Still, the prevalence and incidence of asthma are increasing.

Contemporary research may reveal the solution for this situation. Recent studies have emphasized the importance of treating both the inflammatory and constrictive pathways in asthma. Inhaled corticosteroids have well-documented success in reducing airway inflammation found in asthma, and the 2002 update of the NIH treatment guidelines now recommends low-dose inhaled corticosteroids as the primary therapy for mild persistent asthma in patients of all ages. Additionally, there is a synergistic effect when an inhaled long-acting beta2-agonist is used concurrently with an inhaled corticosteroid for moderate and severe persistent asthma. Thus, the management of asthma using dual-controller therapy may offer the best outcomes for candidate patients, and this is reflected in the updated 2002 NIH guidelines for both adults and children.

Managed care combines the medical and business aspects of health care and must take advantage of the link between clinical and economic outcomes. That is, the best clinical outcomes will usually result in the best long-term economic outcomes. The appropriate use of cost-effective medications, such as dual-controller therapy for candidate asthmatics, may provide superior clinical and economic outcomes. Practitioners in managed care can treat asthma using dual-controller therapy to achieve optimum clinical and economic outcomes. Health plans can use this information to help manage formulary decisions regarding asthma medications and evaluate the clinical and economic impact of asthma management.

ACKNOWLEDGMENT

Dr. Navarro received an honorarium for participating in the symposium on which this article is based. He serves as a consultant and speaker for Aventis, Bayer, Berlex, Eli Lilly, GlaxoSmithKline, Pharmacia, Roche, and Serono.

Target Audience:
Managed care pharmacists and other health care practitioners

Learning Objectives:
Upon completion of this session, the participant will be able to

1. define the categories of asthma severity and summarize the goals of asthma treatment as defined in the NIH Guidelines for the Diagnosis and Management of Asthma;

2. discuss the pharmacologic basis for the concurrent use of a long-acting beta2-agonist and an inhaled corticosteroid in patients with chronic persistent asthma;

3. compare the advantages and disadvantages of randomized clinical trials and retrospective cohort analyses; and

4. illustrate the potential economic impact of using different dual-controller regimens for controlling asthma in a managed care population.
OBJECTIVE: To describe the current status of asthma management in the United States, including the role of the Guidelines for the Diagnosis and Management of Asthma, developed by the National Institutes of Health (NIH), and the Health Plan Employer Data and Information Set (HEDIS) 2000, developed by the National Committee for Quality Assurance (NCQA).

DATA SOURCES: This article is based on a presentation given by the author at a symposium entitled “Optimizing Clinical and Economic Outcomes in Asthma Management” at the Academy of Managed Care Pharmacy’s 2000 Educational Conference in San Diego, California, on October 5, 2000.

CONCLUSIONS: Health care professionals have not yet fully convinced patients that asthma is a chronic disease requiring appropriate medication therapy and routine follow-up care. Asthma is often treated episodically, which is related to increased emergency room visits, hospitalizations, and acute-care visits. The appropriate treatment of asthma incorporates concepts from the NIH guidelines and begins with accurately classifying asthma based on pulmonary function and clinical symptoms. Inhaled corticosteroids (ICSs) are preferred first-line therapy for children as well as adults with persistent asthma. HEDIS 2000 defined a performance measure for asthma with which health care plans can be compared; this measure is based on administrative rather than clinical parameters. Use of fewer canisters of short-acting beta-agonists per year is associated with relatively less risk of hospitalization for patients using ICS; even low-dose ICS therapy is effective in decreasing the asthma death rate.

T he pathophysiology of asthma is increasingly well understood. Asthma is a disease of inflammation and of bronchospasm. Practically speaking, asthma is a chronic disease with intermittent symptoms and frequently episodic therapy. Embodied in that practical description is a primary problem in treating asthma today: episodic or exacerbation-oriented therapy. We understand the importance of peak-flow meters and spirometry for diagnosing and monitoring asthma, yet many physicians who treat asthma do not have a spirometer and have never prescribed a peak-flow meter. This is disconcerting since asthma cannot be accurately classified and treated without pulmonary function information.

Two national-level documents address the treatment of asthma. Guidelines for the Diagnosis and Management of Asthma is an evidence-based document produced by an expert panel first convened by NIH in 1989; it was revised in 1997 and again in 2002. Many specialists believe that asthma treatment is improved when physicians adhere to these guidelines. The Health Plan Employer Data and Information Set (HEDIS) 2000, developed by NCQA, is different in intent from the guidelines. It identifies performance measures on which health care plans can be compared. It defines minimally acceptable therapy for asthma in a single measure.

I will describe the current status of asthma management in the United States and what it represents for the future. The role of the NIH guidelines and HEDIS 2000 document in guiding the direction of therapy will be addressed.

Cost and Demographic Trends

A recent study on the demographics of patients with asthma covers the period from 1985 through 1994. During this time period, the annual cost of treating asthma in the United States almost doubled, reaching close to $11 billion in 1994. Much of that figure includes indirect costs, such as missed time from school and work. The number of prescriptions for asthma increased more than 100% during that 10-year period. The cost of those prescriptions increased from $1.5 billion to well over $2.5 billion annually. In California in 1994, more than $1 billion in costs were attributed to approximately 1.5 million residents with asthma.

According to 1998 and 1999 data, there are 17 million people with asthma in the United States; 57% of them are female. Asthma is not a disease only of childhood. It often starts in childhood, but it is not unusual to see adult-onset asthma. Certainly, children who have asthma often grow into adults who have asthma. Two thirds of the population with asthma is in the adult category (more than 18 years). While the prevalence of asthma in all Americans is 5.5%, for Hispanics it is more than double that (11.2%). The prevalence for Caucasians and African Americans is 4.6% and 6.5%, respectively. The reasons for these differences are not clear.

The estimated distribution of people with asthma according to the severity classifications in the NIH guidelines is as follows: 28%
mild intermittent asthma, 25% mild persistent asthma, 31% moderate persistent asthma, and 16% severe persistent asthma. This suggests that almost 50% of people with asthma have moderate-to-severe persistent asthma and may need inhaled corticosteroid (ICS) therapy combined with an inhaled long-acting beta₂-agonist (LABA). Alternatively, ICS may be combined with a leukotriene modifier or theophylline, as recommended by the 2002 NIH update.

Annually, 5,000 to 6,000 people die from asthma in the United States, and there are approximately 800,000 hospitalizations and 45-50 million exacerbations treated in emergency rooms or clinics. It is not obvious which patients will have poor outcomes. In a study published in 1992, pediatric asthma deaths were reviewed in terms of patient’s family’s perception of asthma severity before the patient’s death. A third of the families thought the patients were mild asthmatics; another third considered the asthma moderate. We believe that patients continue to underestimate the severity of their disease, as they did at the time of this study.

### Opportunities for Closing the Performance Gap

To design asthma therapy and improve outcomes, both patients and providers need goals. According to the NIH guidelines, the goals of asthma therapy are as follows:

- No sleep disruption
- No missed school or work
- No (or minimal) need for emergency room visits or hospitalizations
- Normal activity levels, and
- Normal or near-normal lung function.

I would retile this list as the providers’ goals of asthma therapy. What are the patients’ goals? While this has not been adequately studied, I have found that patients are interested in taking minimal amounts of medication, not having to go to the doctor, and generally not having to think about asthma. Patients understand that hypercholesteremia, hypertension, and diabetes mellitus are chronic diseases that require continuous medication and routine follow-up care. Health care professionals have not completely convinced patients and the public that asthma is also in the chronic disease category. Patients want to view asthma as an episodic disease requiring little treatment during symptom-free periods. It is often treated that way, contributing to overall poor results in therapy.

This lack of understanding is not an isolated sociological phenomenon. Even well-educated patients at a high socioeconomic level often want their medications stopped after their symptoms are controlled for a few months, despite explanations of the chronic nature of asthma.

Table 1 shows the discrepancies between the treatment goals for asthma and patients’ clinical status. The data are from the “Asthma in America” study done in 1998 in which 2,509 asthmatic patients were interviewed by telephone about their health and activity status. The results indicate that this patient group was highly symptomatic. For example, even though the treatment goal is no sleep disruption, 30% of patients were awakened at least once a week by breathing problems. According to the NIH classification of asthma severity (Table 2), patients awakened once a week have mild persistent asthma; more frequent awakening represents moderate persistent asthma. In addition, a large percentage of children and adults with asthma missed school or work because of asthma in the year preceding the study.

Just over one third of patients reported having had a pulmonary function test in the preceding year. Less than 30% had a peak-flow meter, and less than 10% reported using it at least once a week. Many did not use it at all. This study suggests that we have not approached the goal of no or minimal need for emergency room visits or hospitalizations. Of adult asthmatics reporting, 41% sought urgent care from the emergency room, clinic, or hospital in the preceding year.

It takes careful interviewing to get adequate feedback regarding patients’ ability to maintain normal activity levels because often they use other reasons, such as being tired or busy, to explain inactivity. If persistent, one learns that a fairly large number of inadequately treated patients limit sports and recreation activities; a substantial number are limited in daily social activities.

As mentioned previously, patients overestimate their level of asthma control. In a review of patients who reported symptoms that met NIH criteria for moderate persistent asthma, 61% considered their asthma to be well controlled or completely controlled. They appeared willing to tolerate the symptoms. For those who met the criteria for severe persistent asthma, about a third thought they were “controlled.”

It is instructive to view what physicians thought they suggested and what patients thought they heard regarding 5 parameters.

### Table 1: Comparison of Treatment Goals for Asthma and Current Performance

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<th>Current Performance</th>
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<tr>
<td>No sleep disruption</td>
<td>30% of asthma patients awakened by breathing problems at least once a week</td>
</tr>
<tr>
<td>No missed school or work</td>
<td>49% of children and 25% of adults with asthma missed school or work because of asthma in the past year</td>
</tr>
<tr>
<td>No (or minimal) need for emergency room (ER) visits or hospitalizations</td>
<td>32% of all patients with asthma sought urgent care from the ER, clinic, or hospital last year</td>
</tr>
<tr>
<td>Maintain normal activity levels</td>
<td>48% of all patients with asthma were limited in sports and recreation activities, 36% in physical exertion, and 25% in their social activities</td>
</tr>
<tr>
<td>Have normal or near-normal lung function</td>
<td>35% of patients reported having had a lung-function test in the past year, 28% had peak-flow meters to monitor their air flow, and 9% of these reported using it at least once weekly</td>
</tr>
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It is instructive to view what physicians thought they suggested and what patients thought they heard regarding 5 parameters.
involved in good asthma treatment: (1) written treatment plan, (2) use of peak-flow meter, (3) pulmonary function tests (spirometry), (4) follow-up visits, and (5) inhaler use (Figure 1). It is encouraging that a high percentage of both patients and providers thought they had talked about follow-up visits and how to use inhalers. While physicians thought they prescribed peak-flow meters extensively, patients did not seem to recall that.

Two of these parameters that I consider important are written treatment plan and initial pulmonary function tests. Asthma cannot be classified satisfactorily without pulmonary function evaluation. The written treatment plan is important because it focuses both the patient and the physician on actions to take when specific peak-flow readings or clinical events occur. Without a written plan, I believe that it is too easy to fall into an episodic treatment pattern. While the 2002 NIH update noted that data were insufficient to support or refute the benefits of using written treatment plans compared with medical management alone, the expert panel continued to recommend written treatment plans as a way of educating patients about self-management. This is especially important for patients with moderate or severe persistent asthma and patients with a history of severe exacerbations.

Both of these aspects of care are easy to document and measure. If a patient had a pulmonary function test, the provider charged for it, and that charge can be extracted from administrative records. If the physician developed a written plan for the patient outlining medication therapy and steps to take for specific peak-flow readings or symptoms, a copy of the plan should be in the patient’s chart and can be extracted using chart review.

The presence of an adequate written treatment plan was considered as a possible measure for the HEDIS document. For the California Department of Health Services, a goal that 100% of patients with asthma have a written treatment plan was considered, but that was viewed as being overly optimistic. Instead, a lower requirement may be suggested for the first year, followed by 5% increases annually.

Using Guidelines for Making Pharmacotherapy Decisions

The NIH classification of asthma severity shown in Table 2 is the structure upon which therapy is superimposed. While some providers argue that the classification scheme is too difficult to remember, it can be simplified by focusing on the basic parameters: pulmonary function, daytime symptoms, and nocturnal symptoms.

Frequently, referrals indicate that “this patient cannot have asthma because pulmonary function tests are normal, and the patient does not audibly wheeze.” When reviewing pulmonary function test results, one should remember that results are essentially normal in both mild intermittent and mild persistent asthma. In addition, the primary symptom in patients with mild intermittent or mild persistent asthma may be cough rather than wheezing.

Asthma is often a nocturnal disease, and patients who awaken every night or twice a week with symptoms are in need of help. The number of nocturnal awakenings is much more useful referral data than nonspecific descriptions like “bad asthma,” “not so bad asthma,” and “few symptoms.”

The guidelines recommend ICSs as safe, effective, and preferred first-line therapy for infants and children as well as adults with persistent asthma. Cromolyn sodium and leukotriene modifiers are still recommended as alternative treatments for infants and children up to 5 years of age with mild persistent asthma. For moderate and severe persistent asthma, the guidelines recom-
I should note that many years ago it was fashionable to increase the dose of ICSs continually to achieve control. We have learned, however, that the dose-response curve for ICSs is relatively flat, so the beneficial clinical effect does not increase proportionally with dose. The revised guidelines reflect the trend to use dual-con- troller therapy as the way to treat asthma in patients not stable on low- or medium-dose ICSs alone.1,3

Leukotriene modifiers are specific inhibitors of one aspect of the inflammatory cycle. Studies have shown that leukotriene modifiers produce less improvement in flow rate than do ICSs in patients with asthma.1 Only for mild persistent asthma in both adults and young children does the 2002 NIH update recommend leukotriene modifiers as an alternative mono-controller therapy.1 For moderate persistent asthma, alternative treatment includes a leukotriene modifier in combination with low-dose or medium-dose ICSs.

### HEDIS Measure

The HEDIS 2000 measure from NCQA addresses minimally acceptable medications for primary therapy in long-term asthma control. It is a performance measure rather than a guideline, and it is not specifically meant to comment on the NIH guidelines nor to supercede them.

For a number of reasons, the HEDIS 2000 asthma measure was designed to be a “low-bar” standard. While we consider optimal therapy to be NIH-guideline oriented, we opted for minimally acceptable therapy in HEDIS because data from across the country suggested that many plans might not have satisfactory ratings if we expected therapy to strictly follow NIH guidelines. Considering the less challenging description of acceptable care in the measure, plans that rate low in this category may need remedial work. Once the first year’s data are available and validated, this measure may be redesigned.

The final section of the HEDIS 2000 document contains comments related to the measures. Those related to the asthma measure confirm the NIH-guidelines approach for treating asthma3: “Inhaled steroids are the preferred mode of treating asthma. The cromolyns are alternatives for mild persistent asthma. Methylxanthines are an alternative but not preferred therapy for mild persistent asthma. Leukotriene modifiers are classified as alternative therapy for mild asthma.”

### Impact of Treatment Options on Outcomes

A current problem in treating asthma is not that we lack successful strategies but that many now manage therapy so well that patients stop believing they have an ongoing disease. Unlike other specialties in which patients return regularly to attain good long-term outcomes, we see asthma patients in whom short-term improvement is so good that they wonder why they should bother with therapy of any type.

Outcome analysis is increasingly important. There are varied outcome measures for asthma. Clinical outcomes can be classified on the basis of time period studied. Short-term clinical outcomes have to do with peak-flow monitoring, symptom-free days, and use of short-acting beta2-agonists. Medium-term parameters have to do with asthma exacerbations or respiratory health of the patient over a period of months. For a long-term view of clinical outcomes, models of lung-disease progression and how that is modified by drugs will be useful.

Appropriate pharmacoeconomic outcomes are also important to plans, patients, and providers. The number of hospitalizations...
and deaths are 2 important asthma outcomes to consider because of their impact on the cost of care and patient satisfaction.

A study involving 17,000 patients in the early 1990s showed that a patient’s relative risk of being hospitalized increased in direct proportion to the number of prescriptions for short-acting beta2-agonists used per year (Figure 2). The relative risk varied somewhat by age, but the overall message was the same for all age groups.

When these data first appeared, some plans suggested limiting the number of albuterol prescriptions to perhaps 8 a year; once that threshold was reached, the physician would receive a notice advising of the hazards of overuse. Many clinicians think that 8 canisters (1,600 puffs) a year is excessive. Even 5 canisters (1,000 puffs) a year of a reliever drug—a drug that should only be used when a patient is having a symptom breakthrough—amounts to 20 puffs a week. Use of large amounts of short-acting beta2-agonists indicates that a patient’s asthma is unstable; these are patients who may have acute problems. I like to see patients use less than 4-6 puffs a week for symptom breakthrough; if more is required, I adjust controller therapy.

In another study, data from 30,000 patients with asthma from 1975-1991 showed that 77 patients died of asthma, for a death rate of 0.25%. This study reviewed the relationship between the death rate ratio from asthma and the number of canisters of ICSs used per year. As shown in Figure 3, the more ICS used the year before, the less was the chance of dying from asthma. For each additional canister of ICS used, the death rate dropped approximately 20%. This suggests that on a population basis, even low-dose ICS therapy is effective in decreasing the asthma death rate.

Asthma therapeutic concepts today reflect the results shown in these 2 studies: use less short-acting beta2-agonists and treat patients with persistent asthma with ICSs. Such therapy should be more effective, resulting in fewer hospitalizations and emergency visits.

How can current treatment patterns be improved? How do we better educate providers and patients? We continue to work to find answers to these questions. The search involves educational psychology, as well as practical concerns of time available and provider resistance to change treatment approaches. Surveys in California indicate that physicians grow weary of attending industry-sponsored programs that focus on specific drug products; they often do not believe that they have the basis on which to make balanced decisions. To address this problem, it has been suggested that pooled funds contributed by pharmaceutical companies be used to host educational programs featuring impartial speakers. Hopefully, such programs will address asthma treatment in an unbiased fashion and may help physicians incorporate suggested changes into their daily practices.

Conclusion

From the perspective of a practicing physician, I see 3 important goals related to the pharmacologic treatment of asthma. The first goal is intelligent use of short-acting beta2-agonists, which means primarily as a reliever drug. The second goal is intelligent use of ICS, which means at least low-dose therapy in patients who have persistent asthma. The third goal is intelligent use of combination therapy in patients who do not respond to low-to-medium dose ICS alone. We have been working toward the first 2 goals for the past 10 years with some degree of success; the latter goal reflects an evolving approach described in this supplement.

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The treatment of asthma has changed dramatically in the last 25 years. When I first started volunteering at a camp for children with asthma in the Los Angeles area in 1976, we used more than 100 injections of subcutaneous epinephrine to get 60 children through the 7 days. In the last 20 years, I cannot recall a single dose of epinephrine being used at camp because nebulized albuterol became the treatment of choice for acute exacerbations. Now since the early 1990s, the number of nebulizer treatments has decreased as the use of inhaled anti-inflammatory agents increased, even in the pediatric age group.

During this same time period, the number of patients taking oral theophylline has dwindled. Of the more than 7,000 patients with asthma in my medical group, only a handful take theophylline. Since the late 1980s, office practice changed from doing finger pricks for determining serum theophylline concentrations to teaching patients how to use spacer devices and peak-flow meters.

In this paper, I will review the basis for these shifts in the therapeutic approach to asthma and the rationale for using dual-controller therapy of an inhaled corticosteroid (ICS) and inhaled long-acting beta2-agonist (LABA) to treat asthma. Although there are 5 ICSs and 2 LABAs available on the market (i.e., formoterol and salmeterol), this review will focus mainly on fluticasone and salmeterol. In addition, the strengths and weaknesses of randomized clinical trials (RCTs) and retrospective cohort analyses using large data sets to compare the clinical and economic outcomes of various treatment approaches will be described. The consistency of the scientific evidence supporting dual-controller therapy with the clinical and economic evidence gleaned from several recent studies will be reviewed. This is especially timely in light of the 2002 update to the NIH guidelines for the diagnosis and treatment of asthma, which recommends dual-controller therapy as preferred treatment in children as well as adults with moderate or severe persistent asthma.1

**Disease of Inflammation**

The cause of asthma and treatment approaches generated a controversy among health care disciplines over the years. Clinicians traditionally focused on using bronchodilator therapy to relieve bronchospasm of asthma. This is understandable given that since the 1920s or 1930s bronchodilation was the only way to bring relief to patients with asthma.

Colleagues in respiratory physiology maintained that the primary problem in asthma was not bronchospasm but rather hyperreactive airway disease. According to them, the lungs of patients with asthma are too twitchy, too sensitive.

Looking at autopsy specimens of patients with asthma, pathologists described asthma as a variant of eosinophilic bronchitis—a...
term used in the literature from the 1930s to 1960s. Considering our current understanding of asthma, it is apparent that our pathology colleagues were closer to the truth.

A series of experiments beginning in the 1970s changed our view of asthma. Researchers developed techniques for performing bronchoalveolar lavage and bronchial biopsies in patients with mild asthma. This work revealed that asthma is a disease of inflammation. Their findings resulted in renewed interest in the inflammatory process and new approaches to treat asthma.

### Pathophysiology of Asthma

One obvious feature associated with asthma is airflow obstruction. Airflow obstruction, however, is not caused solely by bronchospasm. Rather, cellular events that occur during airway inflammation contribute to the bronchoconstriction, such as edema of the wall that narrows the airway and hypersecretion of mucus into the lumen of the airway.

When this inflammatory process continues unabated, anatomical changes in the lung may occur, such as cellular metaplasia and hypertrophy of the submucosal region. The muscle itself becomes thickened, resulting in smooth muscle hypertrophy. Also seen are collagen deposition and subepithelial matrix protein deposition.

Figure 1 shows the key cells involved in the inflammatory response in the airway. Around each cell are listed cytokines and cellular mediators that are released during inflammation.

It is instructive to see how different classes of asthma medications influence the inflammatory process. As shown in Figure 2, leukotriene modifiers influence several mediators at the level of the basophil, mast cell, and eosinophil. Figure 3 shows the effects of beta-adrenergic receptor agonists—effects not appreciated 10 years ago that go beyond the smooth muscle cell. Corticosteroids (inhaled or systemic) have dramatic effects on multiple cells and multiple mediators in the inflammatory process (Figure 4).

The anti-inflammatory effect of ICSs is visible on biopsy. The left half of Figure 5 shows the intense inflammatory response of a pretreatment bronchial biopsy specimen from a patient with asthma. After 3 months of treatment with inhaled budesonide 600 mcg twice daily, the integrity of the epithelial barrier is restored (Figure 5, right). The basement membrane is far better organized, and the cellular element of inflammation is absent.

Eosinophils play a major proinflammatory role in the pathogenesis of asthma. Corticosteroids have been shown to influence eosinophil survival in an in vitro study. Of 5 different ICSs, beclomethasone dipropionate, which was the first ICS available, is the least effective in diminishing eosinophil survival, with a 50% inhibitory concentration (IC50) of 290 nM. Flunisolide and triamcinolone acetonide are intermediate inhibitors with IC50 values of 32 and 25 nM, respectively. The 2 most potent inhibitors of eosinophils are budesonide and fluticasone propionate (IC50 of 8.5 and 2.3 nM, respectively). Since this was an in vitro study, the clinical relevance of these findings is unknown.

### Scientific Rationale for Dual-Controller Therapy

Airway inflammation and smooth muscle dysfunction are interrelated in asthma (Figure 6). In patients who warrant more aggressive treatment, the combination of an ICS and an inhaled LABA, termed dual-controller therapy, works at different levels to prevent asthma symptoms.

In vitro studies have shown that ICSs increase beta2 synthesis and up-regulate the beta2-receptor. This supports clinical experience that overuse of oral or systemic beta2-agonists, which can diminish a patient’s reactivity to subsequent administration of the medication, is reversed by the use of corticosteroids. In addition, LABAs prime corticosteroid receptors to make the receptors more active. Both ICSs and LABAs also enhance eosinophil apoptosis or programmed cell death, which may be one of the important features in halting the inflammatory process in the lung.

Nasal mucosa resembles lower respiratory mucosa. Since nasal mucosa is easily accessible, it is frequently used as a surrogate for respiratory mucosal. Up-regulation of beta2-receptors occurs in nasal mucosa with as little as 3 days of therapy with topical corticosteroid.

The changes in receptors attributed to dual-controller therapy can be seen graphically in Figure 7. In the control on the left, most of the glucocorticoid receptors exist in the cytosol, which is the liquid medium of the cytoplasm. Only a small amount exists in the nucleus. After pretreating these cells with salmeterol, some translocation of the receptors from the cytosol into the nucleus occurs. The effect is more substantial when a corticosteroid is used; in this case, fluticasone propionate. When a LABA is combined with fluticasone propionate, however, there is a dramatic increase in the translocation of the receptor from the cytosol to the nucleus.

Figure 8 illustrates the proposed complementary mechanism of action of salmeterol and fluticasone propionate. The fluticasone molecule is transported across the cell membrane, binds to a receptor that is inactive in the cytoplasm, and must be translocated to the nucleus where it increases messenger RNA, causing the anti-inflammatory response. By adding a long-acting bronchodilator like salmeterol, the beta receptor in the cell membrane moves into the cytoplasm, where it primes the corticosteroid receptor for its interaction with fluticasone, resulting in increased translocation into the nucleus.

Studies of eosinophil survival also support the complementary effect of a LABA with an ICS on eosinophil survival. Amendini et al. showed that the combination of salmeterol and fluticasone propionate had an EC50 (effective dose causing a 50% reduction in eosinophil survival) of 0.05 nM compared with 0.32 nM for fluticasone propionate alone or 4.5 nM for salmeterol alone.

### Asthma Management

Our understanding of the pathophysiology of asthma has enabled
Current Approaches to Asthma Management: Assessing Clinical and Economic Evidence

**FIGURE 3** Effect of Beta2-adrenergic Receptor Agonists on Inflammatory Cells (Used with permission from GlaxoSmithKline.)

**FIGURE 4** Effect of Corticosteroids on Inflammatory Cells (Used with permission from GlaxoSmithKline.)
Current Approaches to Asthma Management: Assessing Clinical and Economic Evidence

us to move away from the symptomatic treatment of bronchospasm into a treatment arena that addresses inflammation as a causative event. The complementary mechanisms of action of LABAs and corticosteroids at the receptor level have been documented, and this forms the basis for the NIH treatment guidelines for moderate and severe persistent asthma. Since most patients with asthma are treated in the primary-care setting, it is not enough for just asthma specialists to understand and use this information. Rather, all primary-care providers, including family practitioners, pediatricians, internists, nurse practitioners, and physician assistants, should apply the NIH asthma treatment guidelines described by Turk across the entire spectrum of care. This is especially important from a population health-management perspective.

There is no way to identify patients, prospectively, who will be high resource users. In the early 1990s, we thought we had an answer when we discovered that 80% of the available resources were being consumed by 20% of the patients with asthma. Using the 80/20 rule, a fix seemed easy: identify the 20% of the patients with asthma using the emergency room and hospital and target interventions specifically for that population; the result would be diminished resource use. Studies showed that resource use for that 20% dramatically decreased during the following year, but the total resource use across the system did not change at all. That is because the 20% who are high-resource users one year will not be the same 20% who are high-resource users the next year. By using guideline therapy for all patients with asthma, physicians treat the entire spectrum of patients with asthma who potentially could increase resource use.

Overall, we are not taking good care of patients with asthma in the United States. Patient compliance may be an issue. Large surveys indicate that two thirds of patients with severe persistent asthma report having an inhaled steroid, but only half of them use it on a regular basis. A patient may use a peak-flow meter for a while, but then stop using it.

Diabetes mellitus and asthma are the most popular diseases from a disease-management perspective. The commonalities are substantial. First, there are nationally accepted guidelines for treatment of both diseases. Also, both asthma and diabetes mellitus have what is termed “low-hanging fruit.” In the case of asthma, the low-hanging fruit is prevention of emergency room visits and hospitalizations. Health care expenditures decrease and the quality of care delivered to patients improves. The same happens for patients with diabetes mellitus when complications involving the eye, heart, kidney, and peripheral vascular system are prevented. Little wonder why these 2 disorders are frequent targets for disease-management programs.

Clinical Evidence Supporting Dual-Controller Therapy

The term “combination therapy” generally has a negative connotation in asthma circles, dating to the days when Marax and Tredral were the mainstay treatment for asthma. Marax (theophylline, ephedrine sulfate, and hydroxyzine hydrochloride; Roerig) is still available; Tredral (theophylline, ephedrine hydrochloride, and phenobarbital; Parke-Davis) was discontinued in 1997. Now we seem to be coming back to this concept of combination therapy, newly named dual-controller therapy.

If a patient takes an ICS and is still exhibiting symptoms, what is the preferred treatment? Options include increasing the dose of the ICS, adding an inhaled LABA, or adding a leukotriene modifier. These options will be examined from the perspectives of symp-
Clinical Effect of Increasing ICS Dose or Adding a LABA

Seven clinical studies in which salmeterol added to an existing dose of ICS was compared with at least doubling the ICS dose in patients with symptoms yielded consistent results.\textsuperscript{9-15} The studies involved a total of 3,326 patients; study size ranged from 274 to 738. Budesonide was used as the ICS in 3 studies,\textsuperscript{9-11} beclomethasone dipropionate in one,\textsuperscript{12} and fluticasone propionate in 3.\textsuperscript{13-15} The study duration varied from 12 to 24 weeks.

All studies demonstrated greater clinical efficacy as measured by peak expiratory flow (PEF) or forced expiratory volume in one second (FEV\textsubscript{1}) and better overall asthma control (decreased symptoms and decreased use of rescue albuterol) when salmeterol was added compared with at least doubling the dose of ICS. In some cases, the ICS dose was 2.5 to 3 times the dose of the ICS taken at baseline.

Looking at one study in detail, all patients were using fluticasone propionate 88 mcg twice daily for a 2 to 4 week run-in period.\textsuperscript{13} Then all patients were randomly assigned to receive either the combination of salmeterol 42 mcg plus this existing dose of fluticasone twice daily or fluticasone propionate 220 mcg twice daily for a 6-month treatment period. As shown in Figure 9, the mean change in peak expiratory flow rate occurred within a month of onset of therapy and was significantly greater at every time point for the combination of salmeterol and low-dose ICS therapy compared with high-dose ICS therapy. Coincident with the improved lung function was the finding that the change in the percentage of symptom-free days was substantially better in favor of the low-dose ICS and salmeterol group (Figure 10). The percentage of days in which rescue albuterol use was not needed mirrored the other 2 parameters.

Matz et al.\textsuperscript{16} specifically looked at the effect on asthma exacerbations of adding an inhaled LABA to ICS therapy in patients who had symptoms versus simply using a higher dose of ICS. An exacerbation was defined as worsening of asthma requiring treatment with oral prednisone. One group of 467 patients took salmeterol 42 mcg and fluticasone propionate 88 mcg twice daily for 24 weeks; the other group of 458 patients took fluticasone propionate 220 mcg twice daily for the same time period. Nine percent of patients in the dual-controller therapy group had at least one exacerbation compared with 14% of patients receiving the increased ICS dose. The total number of exacerbations was 47 in the dual-controller therapy group, for an exacerbation rate of 0.29%. For those receiving the increased ICS dose, the total number of exacerbations was 75 for an exacerbation rate of 0.48%. The mean duration of exacerbation was 8.4±0.9 days and 10.5±1.2 days, respectively.

Since it is optimal to control asthma with a minimum dose of inhaled steroid, it is clear that there are substantial advantages in pulmonary function, diminished rescue medication use, better symptom control, and fewer exacerbations by using the dual-controller approach rather than increasing the dose of ICS.

Clinical Effect of Adding LABA or Leukotriene Modifier to ICS Therapy

Two studies have compared the clinical efficacy of adding either an inhaled LABA or a leukotriene modifier to low-dose ICS therapy.\textsuperscript{17,18} In one study, salmeterol was compared with zafirlukast,\textsuperscript{17} another with montelukast.\textsuperscript{18} Following run-in, the treatment peri-
od was 4 and 12 weeks, respectively.

The results consistently showed that salmeterol plus an ICS was superior to a leukotriene modifier plus an ICS in symptomatic patients for lung function measured as FEV1 or peak flow, symptoms, and rescue albuterol use. In the Nelson et al.18 study, 447 patients took fluticasone propionate 100 mcg twice daily for a 3-week run-in period. Then half of the patients were randomly assigned to take a combination product containing fluticasone propionate 100 mcg and salmeterol 50 mcg twice daily (Advair Diskus, GlaxoSmithKline). The other half received fluticasone propionate 100 mcg twice daily plus montelukast 10 mg daily by mouth.

Nelson et al.18 found that patients taking fluticasone propionate and salmeterol had better lung function, improvement in symptom-free days and rescue-free days, and a significant reduction in asthma exacerbations compared with montelukast plus an ICS. Both treatments were equally well tolerated. Within one week, there was a substantial difference in mean morning PEF for the group receiving the combination of fluticasone propionate and salmeterol, and this continued for the entire 12-week treatment period.

The results of this study abated the concern that chronic use of LABAs may mask symptoms of asthma, resulting in a worsening of asthma exacerbations. In the group receiving salmeterol, only 2% had an exacerbation, defined as having to intervene in some way (generally with a course of oral corticosteroids), compared with 6% in the leukotriene modifier group.

A meta-analysis of 10 studies corroborated the finding that patients treated chronically with LABAs do not experience an increase in severity or frequency of asthma exacerbations.19 In fact, asthma exacerbations decreased after adding salmeterol to ICS therapy compared with increasing the dose of the ICS.

Decreasing ICS Dose
The addition of a LABA has allowed a reduction of the steroid dose in patients with stable asthma without a decline in short-term asthma control. Nielsen et al.20 found that more than 75% of patients who had salmeterol 50 mcg twice daily added to their ICS regimen experienced at least a 50% reduction in ICS use. Fewer than 25% of patients receiving placebo were able to achieve that reduction. Whether the ICS dose reduction can be maintained long term without any deleterious effects remains unknown.

Use of Retrospective Research Designs
Over the past 40 years, our ability to determine whether drugs are safe and effective has improved substantially. Study design has evolved from the concepts of placebo control and randomization to block enrollment with stratification and the use of single-dummies and double-dummies. Wash-ins, run-outs, and crossovers have become common.

Over the past 15 years, 2 parallel developments have added to the information obtained from RCTs. One is the development and validation of quality-of-life instruments used in conjunction with RCTs. The other is the development of pharmacoeconomics. Each of these has strengths and weaknesses, but the results can provide complementary information.

On the experimental side of the continuum of research designs is the RCT, the classic design to determine efficacy (Figure 11).21
RCTs also provide information about safety. Some RCTs provide a hint of economic analysis. Typically, the results of cost-effectiveness studies are of limited value in a real-world setting, however, because the cost is reported in dollars per unit of improvement in FEV₁ or peak flow rate. It is difficult to translate this to meaningful clinical information.

The far right side of the continuum represents strictly observational studies, the most common type being the case study. Intermediate between observational and experimental studies are cohort studies. In this section, I will discuss how cohort studies can be used to answer questions that cannot be answered through RCTs and to provide evidence to support or dispute the results of RCTs. Cohort studies relying on claims analysis can have both prospective and retrospective components. Typically in an RCT, patient eligibility is very narrowly defined through inclusion and exclusion criteria. For instance, one can enroll only patients with a certain level of asthma, judged according to specific severity or symptom criteria. The obvious strength of an RCT is the randomization process, which fairly allocates potential confounding variables to all treatment groups. This results in high internal validity.

There are limitations to RCTs, though. Many have relatively small sample sizes. By using strict exclusion and inclusion criteria and short duration (usually 4 to 12 weeks), the results may have limited relevance to clinical practice in the office setting. Statisticians refer to this as low external validity.

Retrospective cohort analysis is just coming into its own in terms of study design. Using this approach, researchers use administrative data sets to identify cohorts of patients who are receiving alternative therapeutic regimens and then compare the associated pharmacy use, medical use, and costs for each cohort. In this observational study design, investigators do not determine enrollment criteria or assign patients randomly to treatment groups. Since variables are measured at least twice (both backward and forward in the claims record from an index event, such as having a prescription filled for a specific drug), these studies are longitudinal.

The strength of cohort analyses is relevance to real-world clinical practice (thus, good external validity). Plus, they are efficient. Once the method is learned, cohort analyses can be completed quickly, providing swift feedback for clinical decision making at a lower cost than RCTs.

The limitations of retrospective cohort analyses have to be addressed, however. In the retrospective cohort analysis, patient assignment to treatment groups is determined by an index event, such as a physician prescribing or the patient filling a prescription for a specific medication, not by randomization. Since physicians may use certain criteria for deciding to put patients on one therapeutic regimen versus another, it would not be fair to compare those 2 regimens because of confounding variables. A variety of regression analysis techniques, such as multiple linear regression, logistic regression, Poisson regression, or instrumental variables regression, can adjust for these confounding variables. This is probably the most important advance in the last 15 years in the use of pharmacoeconomic data.

Since retrospective analyses rely on existing databases at the administrative level, one must take steps to control for threats to internal validity. This is often done by comparing the accuracy of claims data with the corresponding medical records for a certain percentage of patients.

Just within the past few years, retrospective cohort analyses based on large administrative data sets have been recognized as a useful research tool for making informed decisions about treatment. Concato and colleagues recently wrote, “The popular belief that only RCTs produce trustworthy results and that observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.”

**Economic Evidence Supporting Dual-Controller Therapy**

Recently Stempel et al. completed a research project in which the health care use and costs associated with common dual-controller therapies in the treatment of asthma in patients enrolled in one health plan were evaluated. A summary of the study and results illustrates the consistency of results from basic scientific, clinical, and economic analyses as well as the usefulness of retrospective cohort analyses in clinical decision making. Four other studies of the pharmacoeconomics of dual-controller therapy have also been completed. Collectively, these 5 studies have involved 52 participating health plans and 16.8 million covered lives.

The analyses for all 5 studies were conducted by the individual health plans. The inclusion criterion was a medical claim for asthma with the appropriate ICD9 code of 493.3X. Treatment was specified as at least one prescription filled for the medication of interest during the treatment period.
Outcomes measured include 5 domains of cost: (1) pharmacy; (2) outpatient care, which might include ancillaries; (3) emergency department use; (4) hospitalization; and (5) the total asthma-care charges (the total of the other 4 domains).

Multivariate regression was used to control for potential pre-index confounding variables. Variables typically adjusted for include age, gender, type of health plan, pre-index asthma pharmacy costs, comorbid respiratory conditions, and pre-index use of short-acting beta2-agonists and oral corticosteroids, as well as pre-index hospitalization, emergency department visits, and physicians office visits.

The Stempel et al. study conducted in September 2000 included patients age 4 years or older with asthma who were continuously enrolled for at least 24 months in one of 13 geographically diverse health plans with 2 million covered lives. In the pre-index period, patients used an ICS as single-controller therapy. The index event was the patient’s filling a prescription for either salmeterol or montelukast, which is a leukotriene modifier.

Patients were divided into 3 groups: fluticasone propionate and salmeterol (n=261), ICS (except fluticasone) plus salmeterol (n=361), and any ICS (including fluticasone) and montelukast (n=216).

The mean adjusted pharmacy cost per patient over a 12-month follow-up for the group using fluticasone propionate and salmeterol was very similar to that of the group using another ICS with salmeterol ($578 and $582, respectively). The average pharmacy cost per patient in the group using an ICS plus montelukast was significantly higher at $973/year.

Table 1 shows the percentage of patients in each group visiting emergency departments and requiring hospitalization over the 12-month follow-up. The results mirror the RCTs results regarding exacerbation rates.16-18 The hospitalization rate for all groups was relatively low: 1.1%, 1.9%, and 4.6% for fluticasone/salmeterol, other ICS/salmeterol, and any ICS/montelukast, respectively.

The mean total adjusted asthma-related cost per patient per year for the group of patients taking any ICS and montelukast was $1,539. This was significantly greater than the cost per patient in the fluticasone propionate and salmeterol group ($945) and in the ICS and salmeterol group ($887).

All of these studies except the first had controls for age, gender, preindex asthma costs, preindex asthma pharmacy use, comorbidity, preindex hospitalization, and emergency department visits. Stempel et al. also controlled for provider specialty. Wang et al. had controls for age, gender, and comorbidity only because it was a cross-sectional study with no preindex period. Used with permission from GlaxoSmithKline.
randomized clinical trials.

These results are also consistent with the 2002 update to the NIH guidelines for the diagnosis and treatment of asthma, which recommends dual-controller therapy as preferred treatment in children as well as adults with moderate or severe persistent asthma.3

## Conclusion

Techniques have been developed for addressing economic questions posed by colleagues on pharmacy and therapeutic committees regarding comparable therapies. Information generated by retrospective cohort analyses using large administrative data sets can help us make important decisions about how to treat our patients. The combination of an inhaled corticosteroid and salmeterol possessed clinical and economic advantages over increased doses of inhaled corticosteroid alone or the combination of an inhaled corticosteroid and a leukotriene modifier.

### ACKNOWLEDGMENT

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### REFERENCES


Asthma affects a large percentage of Americans. In 1998, about 17 million people in the United States had this chronic disease, resulting in direct and indirect expenses of approximately $11.3 billion. Many managed care organizations have established disease-management programs for asthma as a way to control costs while providing consistent, high-quality care. These programs are often modeled after the National Institutes of Health guidelines for the diagnosis and management of asthma.

As described by O’Connor and supported by recommendations of the 2002 update to the NIH treatment guidelines, much clinical evidence exists supporting the use of an inhaled corticosteroid (ICS) and an inhaled long-acting beta2-agonist (LABA) to treat both the chronic inflammation and bronchoconstriction of asthma in patients with moderate or severe asthma. Less is known about whether the same results hold true in the general population of asthmatics and whether the improved asthma control translates to cost savings.

This paper describes the results of 2 previously published studies with which I was involved that assessed the cost impact of the most commonly prescribed dual-controller regimens for treating asthma in managed care populations. Phase 1 was a cross-sectional retrospective claims study. Phase 2 was a 2-year retrospective cohort analysis of the efficacy and efficiency of dual-controller therapies.

### Cross-Sectional Study

In the phase 1 cross-sectional study, patients with ICD9 codes for asthma between the ages of 12 and 65 years who were continuously enrolled during the 6-month study period in one of 4 geographically diverse health plans were included. The 4 plans were subsidiaries owned by Health Net, Inc (formerly Foundation Health Systems, Inc.). In 1999, the plan on the West Coast covered more than 2 million members, and the Northeast plan had more than 1 million members. The plans in the Southeast and mid-Atlantic regions together had more than 1 million members. The West Coast plan, which is in the heart of managed care territory, primarily pays providers through capitated contracts, while the other 3 plans use a fee-for-service system. Patients with chronic obstructive pulmonary disease were excluded.

For the West Coast and Northeast plans, data were collected from November 1998 through April 1999. Data collection for the other 2 plans occurred from July 1998 through December 1998. Since asthma is affected by various seasons of the year, these staggered data-collection periods ensure that almost the entire year is covered.

Administrative claims databases were the source of data for...
![Table 1: Characteristics of Patients in Cross-Sectional Comparison of Dual-Controller Regimens*‡

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FP and Salmeterol (n = 967)</th>
<th>ICS (except FP) and Salmeterol (n = 2511)</th>
<th>ICS and LTM (n = 826)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>37.0</td>
<td>39.0</td>
<td>33.8</td>
</tr>
<tr>
<td>Age (year)</td>
<td>43.8 ± 16.0</td>
<td>45.3 ± 17.0†</td>
<td>43.6 ± 16.4</td>
</tr>
<tr>
<td>Presence of comorbidity (%)‡</td>
<td>39.7</td>
<td>41.3</td>
<td>45.6</td>
</tr>
</tbody>
</table>

*Reported as mean (± SD) unless otherwise noted.
†Significantly different than the FP and salmeterol group at P<0.05.
‡Comorbidities include one or more of the following diseases: cardiovascular disease, congestive heart failure, depression, diabetes, emphysema, hyperlipidemia, hypertension, or other respiratory conditions.

![Table 2: Mean Cost ($) per Patient in 6-Month Period in Cross-Sectional Comparison of Dual-Controller Regimens*§

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>FP and Salmeterol (n = 967)</th>
<th>ICS (except FP) and Salmeterol (n = 2511)</th>
<th>ICS and LTM (n = 826)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy</td>
<td>297.1 ± 211.3</td>
<td>352.2 ± 217.0*</td>
<td>385.7 ± 253.4*</td>
</tr>
<tr>
<td>Outpatient</td>
<td>80.58 ± 197.66</td>
<td>87.26 ± 181.18</td>
<td>121.80 ± 219.05*</td>
</tr>
<tr>
<td>Asthma management†</td>
<td>381.6 ± 301.3</td>
<td>452.9 ± 298.4*</td>
<td>500.8 ± 336.5*</td>
</tr>
<tr>
<td>Inpatient</td>
<td>20.9 ± 256.0</td>
<td>16.0 ± 228.5</td>
<td>36.1 ± 406.5</td>
</tr>
<tr>
<td>Emergency department</td>
<td>8.9 ± 76.2</td>
<td>10.7 ± 91.0</td>
<td>10.5 ± 77.5</td>
</tr>
<tr>
<td>Asthma treatment failure‡</td>
<td>29.9 ± 271.3</td>
<td>26.7 ± 259.0</td>
<td>46.6 ± 420.4</td>
</tr>
<tr>
<td>Total§</td>
<td>408.6 ± 401.9</td>
<td>460.3 ± 445.0*</td>
<td>560.8 ± 627.4*</td>
</tr>
</tbody>
</table>

*Significant results compared with fluticasone propionate and salmeterol group using multivariate regressions controlling for age, gender, region, and comorbidities at P≤0.05
†Includes pharmacy and outpatient costs.
‡Includes inpatient and emergency department costs.
§Total is not always the sum of subcategories because of missing data.

The most prevalent comorbid condition was depression (20% of patients). Multivariate analyses controlling for age, gender, plan, and comorbidities were used to estimate the impact of the 3 different regimens on cost.

Table 2 summarizes the mean cost per member for the 6-month study period for patients in the 3 treatment groups for various aspects of care. Hospital, emergency department, and pharmacy costs were determined from their respective data sets, which are highly accurate. Because outpatient care in the West Coast plan was capitated, estimates of statistics requiring outpatient cost data were based on data from the other 3 regions. Asthma management cost is the sum of pharmacy and outpatient costs, which is the plan’s investment in the asthma patient population so that they do not need emergency department visits or hospitalizations. Because inpatient care and emergency department visits should not be necessary if patients are managed properly on an outpatient basis, those costs are summed to give a measure of asthma treatment failure.

The total average asthma care cost for patients taking fluticasone propionate and salmeterol was $409, which was significantly lower (P<0.05) than the cost for other ICS and salmeterol ($460) and ICS and LTM ($561). As shown in Table 2, the source of the lower costs lies in the pharmacy and outpatient costs. The differences across treatment groups for inpatient and emergency department costs were small and not statistically significant.

This study provided just a snapshot of care in 4 managed care plans along with other potential limitations, such as not controlling for race/ethnicity and pretreatment disease severity. The results show that different drug regimens are associated with measurable differences in outcome when both drug costs and use of medical services are taken into account. This study suggests that the fluticasone and salmeterol combination would be preferable to the other 2 regimens in controlling overall asthma care costs.

### Retrospective Cohort Analysis

As phase 2 of this study, we conducted a 2-year retrospective cohort study, again using a large claims database. The purpose of the study was to compare the cost of 3 common dual-controller therapies, controlling for asthma severity by using preindex cost and use measures. We longitudinally followed patients aged 12-65 years with asthma who received an index prescription for one of the dual-controller regimens (salmeterol or LTM) between January 1, 1997, and December 31, 1998. The records of these patients were reviewed for one year before (preindex) and one year after (postindex) the index prescription.

Because of the rigorousness of the study, the sample only included patients from 2 health plans that were subsidiaries of Health Net, Inc., one in the Northeast and the other on the West Coast. Together the 2 plans covered 3.5 million lives.

All patients received at least one prescription for an inhaled corticosteroid in the preindex period. Patients were excluded if...
they had chronic obstructive pulmonary disease or respiratory cancer, resided in a nursing home or intermediate care facility, or used salmeterol or LTM in the preindex period. At the index date, they were switched to dual-controller regimens and categorized into the same 3 groups as used in the cross-sectional study. The n values are smaller than in the previous study: 121 for fluticasone propionate and salmeterol, 844 for ICS (except fluticasone propionate) and salmeterol, and 360 for ICS and LTM.

Table 3 shows the patients’ preindex characteristics. The mean age of patients in the 3 groups ranged from 41 to 47 years, with the fluticasone propionate and salmeterol cohort having a significantly lower age than the other 2 groups. The majority of the patients were female (65-67%). About 80% of patients in the ICS and salmeterol group were enrolled in the West Coast plan. The lower use of this drug combination in the Northeast plan was a result of restricted formulary status for fluticasone propionate during the beginning of the study period, not of an asthma management program. Emergency department cost and medical asthma cost (sum of outpatient, inpatient, and emergency department) were highest in the fluticasone propionate and salmeterol group. In the regression modeling, preindex cost and use variables were used to control for asthma severity.

Table 4 shows a comparison of costs in the preindex and postindex periods. In all 3 groups, pharmacy cost increased in the postindex period after salmeterol or a leukotriene modifier was added to the ICS. Costs for the emergency department, inpatient care, and outpatient care decreased. Despite the substantially higher emergency department and inpatient costs for the fluticasone propionate and salmeterol group, this cohort of patients had the largest reduction in those costs in the postindex period, resulting in an average increase of $22 in total costs. At the same time, the total cost increased $333 in the ICS and salmeterol group and $378 in the ICS and LTM group.

The fluticasone propionate and salmeterol group still had significant savings in total costs compared with the ICS and LTM group when gender, age, plan type, eligibility, and preindex use and cost variables were controlled using multiple regression. The costs were similar between the fluticasone and salmeterol group and the other ICS and salmeterol group. Using multiple regression in which the cost is adjusted for preindex use and cost variables, the 12-month risk-adjusted total cost for the fluticasone propionate and salmeterol group was the lowest at $975, followed by...
by $1,089 and $1,268 for the ICS and salmeterol and for the ICS and LTM groups, respectively. Pharmacy costs accounted for most of the risk-adjusted total costs ($814, $841, and $996, respectively).

**Conclusion**

Dual-controller therapy consisting of fluticasone propionate and the long-acting beta2-agonist, salmeterol, resulted in lower total asthma care costs than a regimen consisting of an ICS with a LTM.

**ACKNOWLEDGMENT**

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**REFERENCES**


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Optimizing Clinical and Economic Outcomes in Asthma Management: Individualizing Drug Therapy to Address the Dual Components of Asthma

Date: __________________________

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Continuing Education

Optimizing Clinical and Economic Outcomes in Asthma Management:
Individualizing Drug Therapy to Address the Dual Components of Asthma

Please circle the correct answer.

1. According to the NIH guidelines, the goals of asthma treatment include all of the following except
   a. No sleep disruption.
   b. Normal activity levels.
   c. Normal or near-normal lung function.
   d. No more than 2 emergency room visits or hospitalizations per year.
   e. No missed school or work.

2. Asthma is an episodic disease requiring little treatment during symptom-free periods.
   a. True.
   b. False.

3. Parameters of a good asthma treatment plan include
   a. Weight-loss program.
   b. Pulmonary function tests.
   c. Written treatment plan.
   d. Follow-up allergy testing.
   e. Alternatives b and c are both correct.

4. As a performance measure, the asthma measure in HEDIS 2000
   a. Supersedes the NIH treatment guidelines.
   b. Provides a high standard that health plans can aim to achieve.
   c. Provides a measure of minimally acceptable medications for primary therapy in long-term asthma control.
   d. Alternatives a and c are both correct.

5. Possible long-term asthma outcome measures include all of the following except
   a. Number of deaths.
   b. Progression of chronic lung disease.
   c. Number of nighttime awakenings.
   d. Number of hospitalizations.

6. The number of canisters of low-dose inhaled corticosteroids used in the previous year is inversely related to the death rate of patients with asthma.
   a. True.
   b. False.

7. Moderate persistent asthma is characterized by
   a. Daily symptoms.
   b. Nighttime wakening at least twice a week.
   c. Forced expiratory volume in one second of less than 60%.
   d. Alternatives a and b are both correct.

8. Airflow obstruction associated with asthma is caused by
   a. Cellular events occurring during inflammation, such as edema and hypersecretion of mucus.
   b. Aspiration of stomach contents.
   c. Bronchospasm.
   d. Alternatives a and c are both correct.

9. In vitro studies have shown that dual-controller therapy of an inhaled corticosteroid and a long-acting beta₂-agonist works at all of the following levels to prevent asthma symptoms except
   a. Long-acting beta₂-agonists prime corticosteroid receptors to make the receptors more active.
   b. Both inhaled corticosteroids and long-acting beta₂-agonists enhance eosinophil apoptosis.
   c. Inhaled corticosteroids decrease beta₂-agonists synthesis.
   d. Alternatives a and b are both correct.

10. The complementary mechanisms of action of long-acting beta₂-agonists and corticosteroids at the receptor level forms the basis for the NIH treatment guidelines for moderate and severe persistent asthma.
    a. True.
    b. False.

11. To control costs, NIH treatment guidelines should be used for
    a. Patients who use the emergency room for asthma exacerbations more than once a year.
    b. Patients who use more than 8 canisters of albuterol per year.
    c. Patients who exhibit asthma symptoms.
    d. Patients who are hospitalized for asthma at least once per year.
12. If asthma is not controlled by an existing dose of inhaled corticosteroid, studies have shown that the greatest clinical efficacy is achieved by
   a. Adding a long-acting beta₂-agonist to the inhaled corticosteroid regimen.
   b. Doubling the dose of the inhaled corticosteroid.
   c. Adding a leukotriene modifier like zafirlukast or montelukast to the inhaled corticosteroid regimen.
   d. Switching to a different inhaled corticosteroid.

13. Chronic use of long-acting beta₂-agonists may mask symptoms of asthma, resulting in a worsening of asthma exacerbations.
   a. True.
   b. False.

14. All of the following are true of randomized clinical trials except
   a. The randomization process allocates potential confounding variables to all treatment groups, resulting in high internal validity.
   b. Randomized clinical trial is the classic design to determine efficacy.
   c. Strict inclusion and exclusion criteria contribute to small sample size, so the results may have limited relevance to clinical practice.
   d. Cost-effectiveness studies done as part of randomized clinical trials are efficient and provide useful information to clinicians.

15. Which of the following is true about retrospective cohort analyses?
   a. Administrative data sets are used to identify cohorts of patients who are receiving alternative therapeutic regimens, and then the associated pharmacy use, medical use, and costs for each cohort are compared.
   b. The lack of randomization greatly limits the usefulness of study results because confounding variables cannot be controlled.
   c. Internal validity can be checked by comparing the accuracy of claims data with the corresponding medical records for a certain percentage of patients.
   d. Alternatives a and c are both correct.

16. Which of the following appeared to be true in retrospective cohort studies of common dual-controller therapies in the treatment of asthma in patients enrolled in health plans?
   a. Information generated by retrospective cohort analyses using large administrative sets was inconsistent with previous results of randomized clinical trials.
   b. Analysis of variance was used to control for potential pre-index confounding variables such as age, gender, type of health plan, pre-index asthma pharmacy costs, comorbid respiratory conditions, and pre-index use of physician and hospital services.
   c. The risk-adjusted mean cost/patient/month was highest for patients receiving an inhaled corticosteroid and a leukotriene modifier.
   d. The index event was the patient’s filling a prescription for an inhaled corticosteroid.

17. All retrospective claims analyses are cross sectional, evaluating outcome variables at one time.
   a. True.
   b. False.

18. Asthma treatment failure as an outcome variable is the sum of inpatient care and emergency department visits.
   a. True.
   b. False.

19. All of the following appeared to be true about the 12-month risk-adjusted analysis in the longitudinal retrospective cohort analysis described by Legorreta except
   a. Gender, age, plan type, eligibility, and pre-index use and cost variables were controlled using multiple regression.
   b. The ICS and LTM group had significantly less inpatient costs in the post-index period compared with the other groups.
   c. Pharmacy costs accounted for most of the risk-adjusted total costs.
   d. The total costs for the fluticasone propionate and salmeterol group were lower than for the ICS and LTM group and the other ICS and salmeterol group.

20. In devising a retrospective claims analysis, only plans paying providers on a fee-for-service basis can be included.
   a. True.
   b. False.
Program Evaluation

Optimizing Clinical and Economic Outcomes in Asthma Management:
Individualizing Drug Therapy to Address the Dual Components of Asthma

Participant’s name: ___________________________ Date: ________________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the post-test answers.

Scale For Questions 1–4

1 = Not at all
2 = Not very well
3 = Somewhat well
4 = Well
5 = Very well

Scale For Questions 5–12

1 = Poor
2 = Fair
3 = Good
4 = Very good
5 = Excellent

Using the scale above for Questions 1–4, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objectives:

1. Define the categories of asthma severity and summarize the goals of asthma treatment as defined in the NIH Guidelines for the Diagnosis and Management of Asthma.

2. Discuss the pharmacologic basis for the concurrent use of a long-acting beta2-agonist and an inhaled corticosteroid in patients with chronic persistent asthma.

3. Compare the advantages and disadvantages of randomized clinical trials and retrospective cohort analyses.

4. Illustrate the potential economic impact of using different dual-controller regimens for controlling asthma in a managed care population.

5. What is your overall rating of this program? ___

6. How would you rate the pertinence of the program materials to your practice? ___

7. Please rate each of the following program aspects:
   a. Content ___
   b. Clarity ___
   c. Knowledge gained ___

8. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)

   1 = No Change
   2 = 1
   3 = 2
   4 = 3
   5 = 4

   Significant change

9. Please indicate the length of time it took to complete this program: (Circle selection)

   Hours: 1 2 3
   Minutes: 0 15 30 45

10. Please rate the difficulty factor for completing this CE program: (Circle selection)

    Easy     Moderate     Difficult

11. Please rate your willingness to recommend this program to colleagues: (Circle selection)

    Very willing     Willing     Not willing

12. Please indicate which venue you prefer for obtaining continuing education: (Circle selection)

    Written monograph     Slides     Videos     Internet-based

    Live sessions     Other: ___________________________